

# PATENT COOPERATION TREATY

From the  
INTERNATIONAL SEARCHING AUTHORITY

# PCT

To:

see form PCT/ISA/220

## WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing  
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference  
see form PCT/ISA/220

**FOR FURTHER ACTION**  
See paragraph 2 below

International application No.  
PCT/IN2004/000347

International filing date (day/month/year)  
10.11.2004

Priority date (day/month/year)  
20.11.2003

International Patent Classification (IPC) or both national classification and IPC  
C07D401/04, A61K31/4545, A61P31/04

Applicant  
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### 1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☒ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

### 2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

### 3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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**Box No. I Basis of the opinion**

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1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
  - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material:
    - ☐ a sequence listing
    - ☐ table(s) related to the sequence listing
  - b. format of material:
    - ☐ in written format
    - ☐ in computer readable form
  - c. time of filing/furnishing:
    - ☐ contained in the international application as filed.
    - ☐ filed together with the international application in computer readable form.
    - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

**Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 25-35, 47-56 (industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 25-35, 47-56 relate to the following subject matter which does not require an international preliminary examination (*specify*):

**see separate sheet**

- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
  - the written form ☐ has not been furnished
  - ☐ does not comply with the standard
  - the computer readable form ☐ has not been furnished
  - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

**WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY**

International application No.  
PCT/IN2004/000347

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**Box No. IV Lack of unity of invention**

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1. ☒ In response to the invitation (Form PCT/ISA/206) to pay additional fees, the applicant has:
- ☐ paid additional fees.
  - ☒ paid additional fees under protest.
  - ☐ not paid additional fees.
2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose not to invite the applicant to pay additional fees.
3. This Authority considers that the requirement of unity of invention in accordance with Rule 13.1, 13.2 and 13.3 is
- ☐ complied with
  - ☒ not complied with for the following reasons:  
**see separate sheet**
4. Consequently, this report has been established in respect of the following parts of the international application:
- ☒ all parts.
  - ☐ the parts relating to claims Nos.

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**Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

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1. Statement

Novelty (N)	Yes: Claims	2,3,5,12-16,26,27,29,37,38,40,47,48,50
	No: Claims	1,4,6-11,17-25,28,30-36,39,41-46,49,51-56
Inventive step (IS)	Yes: Claims	
	No: Claims	1-56
Industrial applicability (IA)	Yes: Claims	1-24,36-46
	No: Claims	

2. Citations and explanations

**see separate sheet**

**Re Item III**

Claims 25-35 and 47-56 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

**Re Item IV**

The common structural feature of the compounds according to claim 1 of the present application is represented by formula I and II. This unit is, however, known from the document D1 (WO 03/050107 A, cf. claim 4, claim 25, Examples 12, 18, 19 and 103 to 108), which is considered as the closest state of the art for the present application. Furthermore, the common feature of the hydrochloride salts A3 and A4 as well as the common feature of the methane sulfonate salts B1 and B2 according to the claims of the present application resides in that they are polymorph forms of the same compound. At least "alternative" polymorph forms of these two salts are also known from the document D1 - for the racemates and two pure enantiomers. D1 discloses two polymorph forms of the hydrochloride (A1 and A2, Examples 103-108) and one polymorph form of the methane sulfonate (Example 12, 18 and 19). Additionally, the compounds of the present application are encompassed by D1. Claim 4 of D1 lists the hydrochlorides and the methane sulfonates and reads "... and its polymorphs" for each compound (page 157, line 15 - page 158, line 2). The compounds of D1 possess the same qualitative activity as those of the application (cf. page 1, line 9-12). A single general inventive concept (Rule 13(1) PCT) between the different salts, polymorphs and isomers is thus not detectable. This single inventive concept is defined as "involving one or more of the same or corresponding special technical features" (Rule 13(2) PCT), which serve to distinguish the current application from the prior art (establishes novelty) and are responsible for the inventive activity.

At least the following inventions must be considered as non-unitary (Rule 13(1) and (3) PCT):

1. subject-matter relating to A-3 compounds

2. subject-matter relating to A-4 compounds
3. subject-matter relating to B-1 compounds
4. subject-matter relating to B-2 compounds

**Re Item V**

**1. PRIOR ART**

Reference is made to the following document:

D1: WO 03/050107 A

**2. NOVELTY**

The subject-matter of the claims cannot be considered to be novel (Article 33(2) PCT). The compounds of the present application are encompassed by claim 4 of D1 (page 157, line 15 - page 158, line 2). The essential structural difference between the claimed racemate and R-(+) of the A3 form and the compounds of Examples 103, 104, 107 and 108 of D1 (A1 and A2 form) resides in the nature of the crystal structure; the difference is confirmed by x-ray spectra. A new selection vis-a-vis D1 can be acknowledged. However, the S-(-) of the A3 form appears to be identical with the S-(-) of the A2 form as disclosed in Examples 105 and 106 of D1 (cf. figure 6 and 9 of the present application as well as the data given in claim 25 of D1 for S-(-) A2 and in present claim 1 for S-(-) A3).

(It should be noted, that there appears to be confusion between the spectra (and data) for compounds S-(-) A3 and S-(-) A4, because according to the spectra S-(-) A4 appears to be the enantiomer of R-(+) A3. In case of such a confusion, the S-(-) A2 of D1 is relevant for S-(-) A4 and not for S-(-) A3 of the present application.)

D1 does not contain spectra of the mesylate compounds. In the absence of any data distinguishing the B1 and B2 form these mesylate compounds, the subject-matter of the present application relating to the B1 and B2 form are considered to be anticipated by the mesylate compounds of claim 4 and Examples 12, 18 and 19 of D1.

### **3. INVENTIVE STEP**

The subject-matter of the claims does not fulfil the requirements of Article 33(3) PCT. The closest state of the art for the present application is represented by D1. D1 discloses structurally similar compounds having antibacterial properties which encompass the present application, because claim 4 of D1 reads "and its polymorphs" (page 157, line 15 - page 158, line 2). For any novel subject-matter of the present application, the structural variation is alleged to lead to alternative derivatives with the same qualitative activity as those described in D1. In view of the experimental part and the other information as given in the description, it can be assumed that this problem has been solved. The problem underlying the present application can, however, not be seen in the provision of further novel derivatives, because the proposed solution would be seen as obvious. In view of the extremely close structural relationship to the compounds of D1 it is considered that the man skilled in the art would regard the new compounds of this application as being obvious alternatives to the known compounds. Especially because the new compounds fall within the generic teaching of D1. Therefore, the problem underlying the present application should be seen in the provision of new derivatives having unexpected properties over those of the closest prior art compounds (D1). In the absence of comparative test results or other appropriate information it is not possible to decide whether such a problem has been solved or not.